California Department of Health Services, Newborn Screening Program
MS/MS Research Project
Descriptions of Disorders Detectable via MS/MS
Using Newborn Screening Dried Blood Spots

Notes:
- *Diagnosis and management of these disorders should be coordinated with a designated Metabolic Center.*
- *These treatment guidelines are general and not comprehensive.*
- *Special medical diets require prescription adjustments and ongoing follow-up with a Metabolic Center.*

AMINO ACID DISORDERS

Disorder: Argininemia

AKA: Arginase Deficiency

Diagnostic Metabolites on MS/MS Screen	Increased arginine.
Enzyme Defect	Deficiency of arginase I
Diagnostic Tests	• Plasma amino acids • Urine amino acids • Urine organic acids • Plasma ammonia
Symptoms if untreated	Hyperammonemia, protein intolerance, episodic vomiting, neurologic damage if undiagnosed and possible death.
Treatment	• Low protein diet, restricted in arginine (Special medical diet) • Sodium phenylbutyrate

Disorder: Argininosuccinic Aciduria

AKA: Argininosuccinic acid lyase (ASAL) deficiency, Argininosuccinase deficiency

Diagnostic Metabolites on MS/MS Screen	Increased citrulline. [Increased glutamine, argininosuccinate, and ammonia not detected on screen]
Enzyme Defect	Deficiency of the enzyme argininosuccinate lyase (ASAL).
Diagnostic Tests	• Plasma amino acids • Urine amino acids • Urine organic acids • Plasma ammonia
Symptoms if untreated	Hyperammonemia, lethargy, vomiting, hypothermia, hyperventilation, hepatomegaly, trichorexis nodosa (brittle hair; pili torti), coma and death.
Treatment	• Low protein diet (Special medical diet). • Arginine supplementation

Disorder: Citrullinemia

AKA: Arginosuccinic acid synthetase (ASAS) deficiency

Diagnostic Metabolites on MS/MS Screen	Increased citrulline [Increased glutamine and ammonia not detected on screen]
Enzyme Defect	Deficiency of the enzyme argininosuccinic acid synthetase.
Diagnostic Tests	• Plasma amino acids • Urine amino acids • Urine organic acids • Plasma ammonia
Symptoms if untreated	Clinical picture varies: hyperammonemia, vomiting, diarrhea and numerous neurological complications including mental retardation, hypotonia, lethargy, coma, seizures and death can occur.
Treatment	• Sodium benzoate and/or sodium phenylacetate • Supplementation with arginine • Protein restriction (Special medical diet)

Disorder: Hepatorenal Tyrosinemia

AKA: Hereditary tyrosinemia, Congenital tyrosinosis, Tyrosenimia Type 1, Fumarylacetoacetate hydrolase (FAH) deficiency

Diagnostic Metabolites on MS/MS Screen	Increased methionine, increased tyrosine [succinylacetone not detected on screen]
Enzyme Defect	Deficiency of enzyme fumarylacetoacetate hydrolase (FAH)
Diagnostic Tests	• Plasma amino acids • Urine organic acids • Urine amino acids, Renal function tests, Liver function tests, Coagulation times
Symptoms if untreated	Liver failure with cirrhosis, ascites, jaundice, coagulopathy; hepatomas, renal enlargement, renal tubular dysfunction (Fanconi syndrome), rickets, neurologic porphyria-like crises; "boiled cabbage" odor
Treatment	• Phenylalanine and tyrosine restriction (Special medical diet). • NTBC (inhibitor of 4-hydroxyphenylpyruvate dioxygenase) to decrease formation of fumaryl-acetoacetate. • Liver transplant if NTBC is ineffective.

Disorder: Homocystinuria

AKA: Cystathionine beta synthase (CBS) deficiency

Diagnostic Metabolites on MS/MS Screen	Increased methionine [Homocyst(e)ine not detected on screen]
Enzyme Defect	Enzymatic defect in the methionine transulphuration pathway. [Note- other defects in methionine remethylation (MTHFR, methionine synthetase, etc.) will not be detected by elevated methionine.]
Diagnostic Tests	• Plasma amino acids • Plasma total homocysteine • Urine organic acids
Symptoms if untreated	Clinical manifestations include skeletal and ocular problems, mild to moderate mental retardation in some instances; thromboembolism and osteoporosis may also occur
Treatment	• Methionine restriction with cystine supplementation (Special medical diet) • Betaine supplementation • Vitamin B_6 may benefit milder forms

Disorder: **Maple Syrup Urine Disease** **AKA:** MSUD, Branched chain ketoaciduria, Branched chain ketoacid decarboxylase deficiency	
Diagnostic Metabolites on MS/MS Screen	Increased leucine/ isoleucine, increased valine [Alloisoleucine not detected on screen]
Enzyme Defect	Deficient activity of the enzyme complex involved in the oxidative decarboxylation of the alpha-keto acid derivatives of leucine, isoleucine, and valine.
Diagnostic Tests	• Plasma amino acids • Urine organic acids • Serum chemistry panel, CBC
Symptoms if untreated	The infant begins to feed poorly which is followed by vomiting, lethargy, muscular hypertonicity, seizures, coma and death; "maple syrup" odor. May have a later age of onset.
Treatment	• Leucine, isoleucine, and valine restriction (Special medical diet). • Evaluate for possible thiamin responsiveness (rare).

Disorder: **Phenylketonuria** **AKA:** PKU, Phenylalanine hydroxylase (PAH) deficiency, Hyperphenylalaninemia	
Diagnostic Metabolites on MS/MS Screen	Increased phenylalanine, decreased tyrosine
Enzyme Defect	Phenylalanine hydroxylase (PAH) Biopterin synthesis disorders (GTPCH, DHPR, etc.)
Diagnostic Tests	• Plasma amino acids • Urine pterin studies • Bloodspot DHPR assay
Symptoms if untreated	Microcephaly, mental retardation, seizures, autistic-like behavior, and fair-light complexion, hair color and eye color; "mousy/musty" odor
Treatment	• Phenylalanine restriction, tyrosine supplementation (Special medical diet). • Tetrahydrobiopterin supplementation in some

ORGANIC ACID DISORDERS

Disorder: **Beta-ketothiolase Deficiency** **AKA:** 3-Oxothiolase deficiency; BKD	
Diagnostic Metabolites on MS/MS Screen	Increase in C5-OH, C5:1 acylcarnitines
Enzyme Defect	Deficiency of 3-oxothiolase
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Urinary organic acids • Serum chemistry panel
Symptoms if untreated	Recurrent severe ketoacidosis, vomiting, Reyes-like episodes
Treatment	• Low protein diet • Carnitine supplementation • Glycine supplementation

Disorder: Glutaric Acidemia, Type I

AKA: GA type 1

Diagnostic Metabolites on MS/MS Screen	Increased C5DC acylcarnitine
Enzyme Defect	Deficiency of glutaryl CoA dehydrogenase
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Plasma amino acids • Plasma carnitine • Serum chemistry panel
Symptoms if untreated	Macrocephaly at birth; progressive neurological problems (movement disorder), episodes of acidosis/ketosis, vomiting, hepatomegaly.
Treatment	• Low protein diet, restricted in lysine and tryptophan (Special medical diet). • Carnitine supplementation. • Riboflavin supplementation.

Disorder: Hydroxymethylglutaric Acidemia

AKA: 3-hydroxy-3-methylglutaryl CoA lyase deficiency, HMGCoA lyase deficiency

Diagnostic Metabolites on MS/MS Screen	Increased C5OH acylcarnitine
Enzyme Defect	Deficiency of 3-hydroxy-3-methyl-glutaryl CoA lyase
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Urine organic acids • Plasma carnitine • Serum chemistry panel
Symptoms if untreated	Severe metabolic acidosis without ketosis; hypoglycemia with fasting; “cat’s urine” odor
Treatment	• Avoidance of fasting; aggressive intervention when hypoglycemia impending • Restriction of dietary protein (leucine), supplementation with carbohydrate (Special medical diet) • Carnitine supplementation

Disorder: Isovaleric Acidemia

AKA: IVA

Diagnostic Metabolites on MS/MS Screen	Increased C5 acylcarnitine
Enzyme Defect	Deficiency of isovaleryl CoA dehydrogenase
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Plasma amino acids • Plasma carnitine • Serum chemistry panel, CBC
Symptoms if untreated	The clinical course includes poor feeding, acidosis, and seizures with coma and death following quite soon if treatment is not begun; “sweaty feet” odor
Treatment	• Low protein.diet, restricted in leucine (Special medical diet). • Carnitine supplementation • Glycine supplementation

Disorder: 2-Methylbutryl-CoA Dehydrogenase Deficiency

AKA: None

Diagnostic Metabolites on MS/MS Screen	Increased C5 acylcarnitine
Enzyme Defect	Deficiency in 2-methylbutryl-CoA dehydrogenase (2-MBCD)
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Plasma amino acids • Plasma carnitine
Symptoms if untreated	One patient on record
Treatment	• Carnitine supplementation • Dietary isoleucine restriction

Disorder: 3-Methylcrotonylglycinemia

AKA: 3-Methylcrotonyl CoA carboxylase (3-MCC) deficiency

Diagnostic Metabolites on MS/MS Screen	Increased C5 acylcarnitine
Enzyme Defect	Deficiency of the enzyme 3-methylcrotonyl CoA carboxylase May be seen as part of a multiple carboxylase deficiency syndrome
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Plasma amino acids • Plasma carnitine • Serum chemistry panel
Symptoms if untreated	Metabolic acidosis and hypoglycemia. Some may be asymptomatic.
Treatment	• Low protein diet, restricted in leucine restricted diet • Carnitine supplementation • Glycine supplementation

Disorder: Methlymalonic Acidemia

AKA: MMA, Methylmalonyl CoA mutase deficiency

Diagnostic Metabolites on MS/MS Screen	Increased C3 acylcarnitine. Variable increase in C4DC
Enzyme Defect	Defect in methymalonyl CoA mutase or synthesis of cobalamin (B_{12}) cofactor (adenosylcobalamin); at least five distinct biochemical causes of this disorder have been identified
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Plasma amino acids • Plasma ammonia • Plasma carnitine • Electrolytes, Glucose, CBC, Liver function tests
Symptoms if untreated	Life threatening/fatal ketoacidosis and hyper-ammonemia often appears during first week of life; later symptoms include failure to thrive, mental retardation, and episodes of coma with a risk of death
Treatment	• Low protein diet, restricted in isoleucine, valine, methionine, threonine (Special medical diet). • Carnitine supplementation • Cobalamin (vitamin B_{12}) useful in some cases.

Disorder: Propionic Acidemia **AKA:** PA, Propionyl CoA carboxylase (PCC) deficiency	
Diagnostic Metabolites on MS/MS Screen	Increased C3 acylcarnitine
Enzyme Defect	Defect in propionyl CoA carboxylase α or β subunit, or biotin cofactor May be seen as part of a multiple carboxylase deficiency syndrome
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Plasma amino acids • Plasma ammonia • Plasma carnitine • Electrolytes, Glucose, CBC, Liver function tests
Symptoms if untreated	Disorder usually presents acutely with feeding difficulties, lethargy, vomiting and life-threatening acidosis. Seizures and retardation are common.
Treatment	• Low protein diet, restriction of isoleucine, valine, methionine, threonine (Special medical diet). • Carnitine supplementation.

FATTY ACID OXIDATION DISORDERS

Disorder: Carnitine/Acylcarnitine Translocase **AKA:** CACT	
Diagnostic Metabolites on MS/MS Screen	Increased C16, C18:1 acylcarnitines
Enzyme Defect	Deficiency of carnitine translocase
Diagnostic Tests	• Plasma acylcarnitine profile • Plasma carnitine • Urine organic acids • Serum chemistry panel
Symptoms if untreated	Hypoketotic hypoglycemia, hepatomegaly, cardiomyopathy, weakness, cardiorespiratory collapse, death.
Treatment	• None known

Disorder: Carnitine Palmitoyl Transferase Deficiency Type 1 (CPT-1) **AKA:** None	
Diagnostic Metabolites on MS/MS Screen	Increased free carnitine (C0), low or absent long chain acylcarnitines (C16, C18:1)
Enzyme Defect	Deficiency of carnitine-palmitoyltransferase- I
Diagnostic Tests	• Plasma acylcarnitine profile • Plasma carnitine • Urine organic acids • Serum chemistry panel
Symptoms if untreated	Hypoketotic hypoglycemia, hepatomegaly, coma, seizures
Treatment	• Avoidance of fasting, aggressive intervention when hypoglycemia impending • Low fat diet • Medium chain triglyceride supplementation

Disorder: **Carnitine Palmitoyl Transferase Deficiency- Type 2**

AKA: CPT 2

Diagnostic Metabolites on MS/MS Screen	Increased C16, C18:1 acylcarnitines
Enzyme Defect	Deficiency of carnitine palmitoyl transferase II
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Serum chemistry panel
Symptoms if untreated	Severe hypoglycemia hypoketosis, cardiomyopathy, polycystic/dysplastic kidneys in neonatal cases, hepatomegaly, hypotonia, seizures, hyperammonemia
Treatment	• High carbohydrate, limited fat diet

Disorder: **Carnitine Transporter Deficiency (systemic carnitine deficiency)**

AKA: None

Diagnostic Metabolites on MS/MS Screen	Decreased free carnitine ("C0 acylcarnitine")
Enzyme Defect	Defect of carnitine transporter
Diagnostic Tests	• Plasma carnitine • Plasma acylcarnitine profile • Urine organic acids • Serum chemistry panel
Symptoms if untreated	Hypoketotic hypoglycemia, cardiomyopathy, skeletal myopathy, sometime liver dysfunction and hyperammonemia
Treatment	• Carnitine supplementation

Disorder: **Glutaric Acidemia Type 2**

AKA: Multiple acyl CoA dehydrogenase deficiency (MADD), GA2

Diagnostic Metabolites on MS/MS Screen	Increased C4, C5 ± C5-DC acylcarnitines [older patients have variable increase of several other acylcarntines]
Enzyme Defect	Deficiency of electron transfer flavoprotein (ETF) or electron transfer flavoprotein dehydrogenase (ETF-DH)
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Plasma amino acids • Plasma ammonia • Serum chemistry panel
Symptoms if untreated	Severe neonatal form: hypoglycemia, hyperammonemia, hepatomegaly, cardiomyopathy, "sweaty feet" odor, often with polycycstic kidneys Later onset form generally milder, may have hypoglycemia, Reye-like symptoms
Treatment	• Avoidance of fasting; aggressive intervention when hypoglycemia and/or acidosis impending. • Regulation of dietary fat intake • Carnitine supplementation • Riboflavin supplementation

Disorder: **Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD)**

AKA: None

Diagnostic Metabolites on MS/MS Screen	Increased C8-C10 acylcarnitines
Enzyme Defect	Deficiency of medium chain acyl CoA dehydrogenase
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Plasma carnitine • Serum chemistry panel
Symptoms if untreated	Fasting intolerance, hypoglycemia, hyperammonemia, acute encephalopathy, cardiomyopathy, liver failure
Treatment	• Avoidance of fasting; aggressive intervention when hypoglycemia impending. • Carnitine supplementation • Regulation of dietary fat intake

Disorder: **3-OH Long Chain Acyl CoA Dehydrogenase Deficiency (LCHADD)**

AKA: None

Diagnostic Metabolites on MS/MS Screen	Increased C16OH, C18:1OH, C18OH acylcarnitines
Enzyme Defect	Deficiency of long chain hydroxyacyl CoA dehydrogenase, or the mitochondrial trifunctional protein
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Serum chemistry panel
Symptoms if untreated	Clinical variability: hypoglycemia, vomiting, lethargy, coma, seizures, hepatic disease, cardiomyopathy, rhabdomyolysis, progressive neuropathy; in some older patients, pigmentary retinopathy
Treatment	• Avoidance of fasting; aggressive intervention when hypoglycemia impending • Medium chain triglyceride supplementation

Disorder: **Short Chain Acyl CoA Dehydrogenase Deficiency (SCADD)**

AKA: None

Diagnostic Metabolites on MS/MS Screen	Increased C4 acylcarnitine
Enzyme Defect	Deficiency of short chain acyl CoA dehydrogenase
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Urine acylglycines
Symptoms if untreated	Lethargy, vomiting, delayed development, muscle weakness, hypotonia. May be asymptomatic.
Treatment	• Avoidance of fasting; aggressive intervention when hypoglycemia impending. • Carnitine supplementation • Regulation of dietary fat intake

Disorder: **Very Long Chain Acyl CoA Dehydrogenase Deficiency (VLCADD)**

AKA: None

Diagnostic Metabolites on MS/MS Screen	Increased C14, 14:1, 14:2 acylcarnitines
Enzyme Defect	Deficiency very long chain acyl CoA dehydrogenase
Diagnostic Tests	• Plasma acylcarnitine profile • Urine organic acids • Serum chemistry panel
Symptoms if untreated	Hypoketotic hypoglycemia with cardiomyopathy and/or liver failure; rhabdomyolysis
Treatment	• Avoidance of fasting; aggressive intervention when hypoglycemia impending • Medium chain triglyceride supplementation • Carnitine supplementation (controversy regarding high doses)

Submitted

Guidelines Committee, California MS/MS Project: S. Cederbaum, B. A. Barshop, M. Lipson, S. Levine, W. Wilcox, S. Winter.

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